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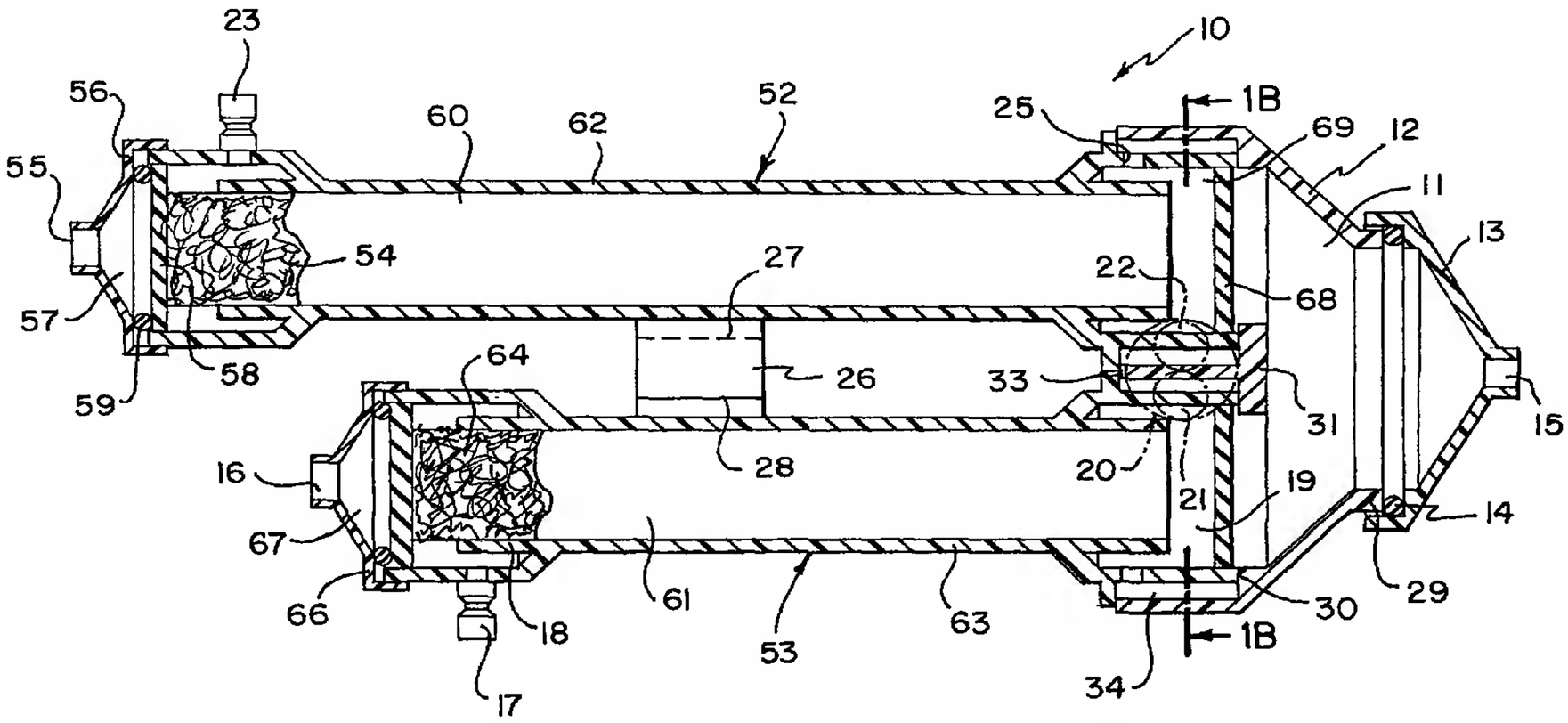
Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: DUAL STAGE HEMODIAFILTRATION CARTRIDGE



(57) Abstract: A dual-stage hemodiafiltration cartridge (10) includes a first hemodiafiltration stage (52) having a housing (62), blood inlet (55), dialysate outlet (23), and first hollow fibers (54); and a second hemodiafiltration stage (53) having a housing (63), blood outlet (16), dialysate inlet (17) and second hollow fibers (64). An inter-stage connector (12) connected to an end of each of the housings includes a header space adapted to allow flow of blood from the blood side of the first hollow fibers (54) to the blood side of the second hollow fibers (64). An inlet (15) allows substitution fluid to flow into the header space to dilute the blood therein. An interdialysate port (20) allows the dialysate to flow from the second hemodiafiltration stage (53) to the first hemodiafiltration stage (52).

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DUAL STAGE HEMODIAFILTRATION CARTRIDGE

Field of the Invention

The present invention relates to hemodiafiltration devices and methods and, more particularly, to a new hemodiafiltration cartridge and its method of use.

Background of Invention

Current treatment for End Stage Renal Disease (ESRD) essentially consists of hemodialysis process, wherein blood to be cleaned flows on one side of a semipermeable membrane and a physiologic solution, a dialysate, flows on the other side of the membrane, whereby toxins in the blood are transferred from one side to the other. The primary driving force in this treatment is diffusion. This process is generally effective in removing small Molecular Weight (MW) toxins such as urea and creatinine. However, this process is much less effective in removing middle range MW substances, e.g., substances having a molecular weight higher than about 1 kDa, because of a low diffusion coefficient of such substances.

To a much lesser extent hemodiafiltration is used as a treatment modality. In hemodiafiltration, diffusion is combined with filtration to remove toxins from the blood. Sterile non-pyrogenic replacement fluid is added to the blood either prior to or after it enters a hemodiafiltration cartridge. The replacement fluid replaces plasma water which is filtered across the semi-permeable membrane during the hemodiafiltration process. The advantage of hemodiafiltration over hemodialysis is the use of filtration in conjunction with diffusion to remove toxins. As a result of this combination, hemodiafiltration is more efficient at removing small molecules, e.g., creatinine and urea, as well as removing much greater quantities of middle range MW substances, by filtration.

State of the art designs for hemodiafiltration filters are substantially equivalent to those of high flux dialyzers. Such filters consist of bundles of hollow fibers in a cylindrical housing. During operation of the hemodiafiltration system, replacement fluid is injected into the blood either upstream (pre-dilution) or downstream (post-dilution) of the filter cartridge.

Diafiltration devices using pre-dilution or post-dilution schemes have inherent efficiency limitations. Pre-dilution schemes allow for relatively unlimited filtration, however, because the blood is diluted prior to reaching the filter, the overall mass transfer of solutes is decreased. Post-dilution schemes have the advantage of keeping blood concentrations high, resulting in more efficient diffusion and convection of solutes, however, the increased concentration of blood cells and the resultant higher blood viscosity during filtration, poses a limit on the amount of water that can be filtered.

Summary of Invention

It is an object of some aspects of the present invention to provide a hemodiafiltration cartridge that enables a higher toxin removal rate and higher toxin removal efficiency than that of prior art hemodiafiltration devices. The present invention reduces and/or eliminates the above mentioned drawbacks of prior art hemodiafiltration devices by providing a scheme in which blood is diluted after it is partially, but not fully, diafiltered. The scheme of the present invention combines the benefits of pre-dilution schemes, e.g., high filtration rate, with the benefits of post dilution schemes, e.g., high diffusive and convective efficiencies. The device of the present invention may be adapted to operate in conjunction with a dual-stage hemodiafiltration machine, or a standard dialysis machine using dual-stage

hemodiafiltration, such as the machines described in PCT patent application No. PCT/US99/17468 and in PCT patent application No. PCT/US99/25804, assigned to the assignee of the present application, the disclosures of both of which are incorporated herein by reference in their entirety. Alternatively, by making appropriate alterations in a dual-stage device according to the present invention, e.g., by allowing direct flow of dialysate fluid between the two stages of the dual-stage device, the present invention may be adapted for use in conjunction with a standard dialysis machine using single stage diafiltration.

A hemodiafiltration cartridge in accordance with the present invention has blood and dialysate inlet and outlet ports. The cartridge of the present invention includes two housings, for example, two cylindrical housings, corresponding to two hemodiafiltration stages, wherein the first stage has a blood inlet and a dialysate outlet, and the second stage has a blood outlet and dialysate inlet.

In an embodiment of the present invention, the blood inlet and outlet ports and the dialysate inlet and outlet ports are located on one side, e.g., at the top, of the cartridge. Each of the two hemodiafiltration stages of the present invention may contain longitudinal bundles of high flux, semi-permeable, hollow fibers, which may be sealed off from the dialysate compartments at each end by a potting compound such as polyurethane. The blood inlet may include a header member that may be attached to a casing of the cartridge, at the fiber ends.

In one embodiment, the two stages are produced separately and then assembled together. Alternatively, the two stages may be manufactured as a single unit. The method of production does not affect the resultant dual-stage cartridge.

In an embodiment of the present invention, the cartridge includes two additional ports, preferably at the

second end, e.g., the bottom end, of the cartridge. One of these additional ports may be a substitution fluid inlet where sterile replacement fluid is mixed with the blood. This mixing may take place in a common header space, between the first and second stages, where the blood exits the hollow fibers of the first stage and enters the fibers of the second stage.

The other additional port may be an inter-dialysate port, for example, a dual aperture port, which directs dialysate fluid exiting the second stage of the cartridge to cycle through the controlling machine, where the flow rate of the dialysate may be metered, and returns the dialysate to the first stage. While the total level of filtration of the cartridge is generally controlled by the dialysate inlet and outlet rates, the inter-dialysate port enables control of the individual filtration rates of the two cartridge stages. This port may also enable modification of the dialysate flow rate or dialysate composition between the two stages. In an alternative embodiment of the invention, the dialysate fluid exiting the second stage may be directed to flow directly into the first stage, e.g., by providing an aperture-connecting cap to the dual-aperture port.

Brief Description of the Drawings

Fig. 1A is a schematic, cross-sectional, front view, illustration of a dual stage hemodiafiltration cartridge in accordance with one preferred embodiment of the present invention; Fig. 1B is a schematic, cross-sectional, top view, illustration of the dual stage hemodiafiltration cartridge of Fig. 1A, taken along section line 1B-1B;

Fig. 2A is a schematic, cross-sectional, front view, illustration of a dual stage hemodiafiltration cartridge in accordance with another preferred embodiment of the present invention;

Fig. 2B is a schematic, cross-sectional, top view, illustration of the dual stage hemodiafiltration cartridge of Fig. 2A, taken along section line 2B-2B;

Fig. 2C is a schematic, cross-sectional, side view, illustration of the dual stage hemodiafiltration cartridge of Fig. 2A;

Fig. 3A is a schematic, cross-sectional, top view, illustration of the dual stage hemodiafiltration cartridge of Fig. 1A, taken along section lines 1A-1A, showing connection of an inter-dialysate port of the cartridge to a hemodiafiltration machine; and

Fig. 3B is a schematic, cross-sectional, top view, illustration of the dual stage hemodiafiltration cartridge of Fig. 1A, taken along section line 1A-1A, showing connection of a inter-dialysate port of the cartridge to an aperture-connecting cap.

Detailed Description of Preferred Embodiments

Reference is made to Figs. 1A and 1B which schematically illustrate a cross-sectional front view and a cross-sectional top view, respectively, of a dual stage hemodiafiltration cartridge 10 in accordance with one preferred embodiment of the present invention. Cartridge 10 includes a first stage 52 and a second stage 53. Stages 52 and 53 preferably include generally cylindrical housings, 62 and 63, respectively, of a rigid plastic material. Housings 62 and 63 contain longitudinal bundles of semipermeable hollow fibers 54, as are known in the art. The semipermeable fibers serve as a means for transferring the toxins which are being filtered from the blood.

In an embodiment of the present invention, cartridge 10 is adapted to operate in conjunction with a dual stage-hemodiafiltration machine, or a standard dialysis machine using dual-stage hemodiafiltration, such as the machines described in PCT patent application No. PCT/US99/17468

and/or in PCT patent application No. PCT/US99/25804, the disclosures of both of which are incorporated herein by reference in their entirety.

During operation, blood transferred from the patient, via a blood pump of a dual stage hemodiafiltration machine, enters first stage 52 of cartridge 10 through an inlet port 55 which is preferably formed in a header cap 56 mounted on an inlet end of housing 62. Cap 56 defines an inner header space 57 which may be separated from the rest of the cartridge by a potting compound 58, which forms a seal around the outside surfaces of hollow fibers 54. Header cap 56 may be removable and, in such case, header space 57 is preferably sealed from the external environment by a sealing member, such as an O-ring 59.

As blood traverses down the insides of fibers 54, along a main filtration space 60 of first stage 52, the outsides of fibers 54 are immersed in dialysate. This results in first stage hemodiafiltration of toxins, i.e., both filtration and diffusion, which takes place along the entire length of fibers 54 within filtration space 60. In an embodiment of the present invention, a significant portion, e.g., approximately 40%-60%, of the plasma water is filtered as the blood flows through first stage 52. The partly hemodiafiltered blood exiting first stage 52 enters an inter-stage header space 11 associated with another end of housing 62. The blood entering inter-stage header space 11 is in a hemoconcentrated state, i.e., the level of hematocrit in the blood is increased. In accordance with an embodiment of the invention, filtration space 60 of first stage 52 and a filtration space 61 of second stage 53 are separated from header 11, for example, by a potting compound 68, in analogy to the separation described above with reference to header space 57 and potting compound 58.

Inter-stage header space 11, which acts as a transition stage for blood exiting first stage 52 and

entering second stage 53, is defined by a stage connector 12 which is preferably made from rigid plastic material and is attached to both the outlet end of first stage 52 and the inlet end of second stage 53, for example, by bonding or welding. Stage connector 12 encloses and defines header space 11 as well as two separate dialysate spaces, 19 and 69. A removable inter-stage header cap 13 having an inlet port 15 is attached to stage connector 12. Header space 11 may be sealed from the external environment by a sealing member, for example, an O-ring 14.

The blood residing in header space 11 prior to entering second stage 53, is diluted with a physiological sterile solution that enters cartridge 10 via header inlet port 15. The sterile solution may be produced continuously, in an "on-line" manner, or provided from reservoirs, e.g., saline bags, as are known in the art. The blood in inter-stage space 11 is hemodiluted, i.e., the blood hematocrit level is decreased. The hemodiluted blood is then carried by fibers 64 disposed in second stage 53, in a manner similar to that described above with reference to first stage 52. At second stage 53 the blood undergoes further hemodiafiltration. The outlet end of second stage 53 is capped with a header cap 66, defining a header space 67 therein, having a blood outlet port 16, in analogy with the above description of header cap 56.

In an embodiment of the present invention, the blood is diafiltered by cartridge 10 at such a rate so that upon exiting second stage 53, via a blood outlet port 16, the blood hematocrit level is substantially the same as that of the blood entering first stage 52. As in standard hemodialysis processes, small changes in the blood hematocrit level may be required in order to control the net ultrafiltration, as may be necessary to maintain patient fluid balance.

As in standard dialysis processes, the dialysate in

the present invention is perfused through cartridge 10 in a "counter-current" direction relative to the flow of blood. The dialysate enters second stage 53 via a dialysate inlet 17. A flow disperser 18 ensures that the dialysate will better perfuse the fiber bundle in second stage 53. An inter-dialysate port 20 is preferably associated with dialysate exit region 19 of second stage 53 and with dialysate inlet region 69 of fist stage 52. Inter-dialysate port 20 (shown more clearly in Fig. 1B) is preferably a dual-aperture port including a second stage outlet 21 and a first stage inlet 22.

Reference is now made also to Fig. 3A which schematically illustrates a cross-sectional side view of cartridge 10, showing connection of inter-dialysate port 20 to a hemodiafiltration machine 71, and to Fig. 3B which schematically illustrates a cross-sectional side view of cartridge 10, showing connection of inter-dialysate port 20 to an aperture-connecting cap 73. Machine 71 is preferably a dual-stage hemodiafiltration machine as described. As shown in Fig. 3A, inter-dialysate port 20 may be connected to machine 71 using a dual-aperture connector 24 which is adapted to fit connections 72 on hemodiafiltration machine 71.

In an embodiment of the present invention, hemodiafiltration machine 71 is adapted to monitor the flow and/or dialysate pressures between the first and second stages of cartridge 10. For example, the hemodiafiltration machine may include an inter-dialysate pump (not shown), which may be used to monitor the flow between the first and second stages of cartridge 10 and/or the relative dialysate pressures of the two stages. It should be appreciated, however, that machine 71 may include any other suitable mechanisms, as are know in the art, for controlling dialysate pressure and/or flow. The monitoring of inter-stage flow and/or pressure, enables control of the level of

filtration in each of the first and second stages to optimize process efficiency.

Hemodiafiltration machine 71 may also be adapted to monitor and/or control other parameters of the dialysate fluid, between the first and second stages, as described in PCT application No. PCT/US99/17468 and in PCT application No. PCT/US99/25804. For example, the composition and/or salt concentration of the dialysate may be modified between the two stages as described in PCT/US99/25804.

After passing through both hemodiafiltration stages, either directly or via machine 71, as described above, the used dialysate exits cartridge 10 via a dialysate outlet 23 of first stage 52.

Blood inlet and outlet ports 55 and 16, respectively, may be associated with locking connectors, as are known in the art, designed to mate with standard bloodlines. Dialysate inlet port 17 and dialysate outlet port 23 may be associated with standard Hansen connectors, as are know in the art. Substitution fluid inlet port 15 may be associated with a standard luer, e.g., a 6% tapered connector as specified in the ISO 594, adapted to accommodate an IV set, as is known in the art.

To accommodate a dialyzer reuse machines having blood inlet and outlet ports, as are know in the art, substitution fluid inlet port 15 may be capped during reuse. The use of removable header caps 56, 66 and 13, as described above, enables tubesheet cleaning during reuse. Additionally, inter-dialysate port 20 may be fitted with the aperture-connecting cap 73 (Fig. 3B) which allows direct dialysate flow from second stage 53 to first stage 52. Cap 73 seals inter-dialysate port 20 from the external environment while allowing flow of dialysate between dialysate outlet 21 of stage 53 and dialysate inlet 22 of stage 52. Such sealing may be useful during reuse, whereby a dialyzer reuse machine may communicate with cartridge 10

as if it were a standard dialyzer. By allowing direct dialysate flow between the first and second stages, as described above, cartridge 10 may be used in conjunction with a standard dialysis machine, i.e., a dialysis machine designed to operate with a single-stage dialyzer.

A thread or any other suitable locking mechanism, as is known in the art, may be provided on the exterior surface of outlet port 24 to enable tight sealing of port 24 with either the dialysis machine connector 72 or aperture-connecting cap 73.

In the embodiment of Figs. 1A and 1B, the first and second stages may be manufactured separately and assembled together prior to packaging. Each of housings 62 and 63 is stuffed with a fiber bundle as described above, and may be centrifugally potted as is known in the art. A potting compound, for example, polyurethane resin, may be introduced into first stage 52 via dialysate outlet port 23. At the other end of first stage 52, the potting compound may be introduced via a dedicated potting port 25 which is analogous to the opening of a second dialysate port in conventional dialyzers. The assembly procedure for second stage 53 is analogous to that of first stage 52. Thus, standard potting techniques and equipment may be used in the assembly of the cartridge of the present invention.

To complete the assembly process, the potted ends of the fibers are trimmed to form a smooth tubesheet of open fibers, and the two stages are assembled into a single unit. The final assembly may be preformed as follows. The two stages are locked together, for example, using a "tongue in groove" type bond or weld 26, including a male portion 27 on housing 62 and a female portions 28 on housing 53, or vice versa. This arrangement keeps the housings from being twisted out of alignment. Stage connector 12 may be bonded or welded to the two housings, as mentioned above.

Stage connector 12 may includes inter-dialysate port 20 as well as a mating portion 29 for connecting inter-stage header cap 15. Connector 12 may be circumferentially welded or bonded to housings 62 and 63 at several locations.

A first bond may be formed along the flat ends of the outer rims 30 of housings 62 and 63, where the tubesheet may be encased. This bond seals the blood sides of both stages 52 and 53 from the external environment, but allows free flow through the inter-stage header space 11 between stages 52 and 53. The bond is preferably formed along the entire rim of each housing, including a common central mating portion 31.

A second weld or bond may be formed along external flanges 32 of housings 62 and 63. This bond seals the dialysate potting ports from the external environment and forces all the inter-dialysate flow to go through the inter-dialysate port. Here too there is a common central bond 33 that effectively separates the dialysate compartments of the two stages.

Stage connector 12 is preferably designed such that dialysate may flow out of potting port 25 into an external space 34 around the outside of the stage housings, as well as to the central area where inter-dialysate port 20 is located.

Reference is now made to Figs. 2A-2C which schematically illustrate a cross-sectional front, a cross-sectional top view and a cross-sectional side-view, respectively, of a dual stage hemodiafiltration cartridge 110 in accordance with another preferred embodiment of the present invention. Most of the elements of cartridge 110, as shown in the embodiment of Figs. 2A-2C, as well as the features and functions of such elements, are substantially the same as described above with reference to the embodiment of Figs. 1A and 1B. Cartridge 110 is mounted to

a hemodiafiltration machine in the manner described above with reference to the embodiment of Figs. 1A and 1B.

The difference between the two embodiments is primarily in the structure and assembly of the inter-stage section. In the embodiment of Figs. 2A-2C, instead of bonding two separately formed cylindrical housings, a dual-housing structure 35 is molded as a single unit, including a first stage housing 162 and a second stage housing 163, for a first hemodiafiltration stage 152 and a second hemodiafiltration stage 153, respectively. This obviates the need for an inter-stage connector and interlocking web, as described above with reference to the embodiment of Figs. 1A and 1B. These elements of the preceding embodiments are replaced by a common inter-stage molded encasement 37 and a molded web 36, respectively.

Molded structure 35 is preferably formed with an integral, generally circular, end portion 38 which accommodates a removable inter-stage header cap 39. In this arrangement, the entire cross-section of encasement 37 is filled with a potting compound 40, thereby to seal the blood side of the fibers bundled in cartridge 110 from the dialysate side of the fibers. A dual-aperture inter-dialysate port 120, shown particularly in Fig. 2B, is used in this embodiment substantially in the manner described above with reference to port 20 of Fig. 1B. However, in this embodiment, the dialysate of first stage 152 is separated from the dialysate of second stage 153 by a rib member 41 across the entire diameter of inter-stage encasement 37. Rib 41 may be molded to one end 42 of web 36 and sealed to the potting compound at the other end 43.

It will be appreciated by persons skilled in the art that the present invention is not limited to the embodiments described thus far with reference to the accompanying drawing. Rather the present invention is limited only by the following claims.

WHAT IS CLAIMED:

1. A dual-stage hemodiafiltration cartridge comprising:

a first hemodiafiltration stage including a first housing having first and second ends and first filtering elements disposed between the first and second ends, the first end being associated with a blood inlet which allows flow of blood into a blood-side of said first filtering elements and a first dialysate outlet which allows flow of dialysate out of a dialysate-side of said first filtering elements and the second end being associated with a first dialysate inlet which allows flow of dialysate into a dialysate-side of said first filtering elements;

a second hemodiafiltration stage including a second housing having third and fourth ends and second filtering elements disposed between the third and fourth ends, the fourth end being associated with a blood outlet which allows flow of blood out of a blood-side of said second filtering elements and a second dialysate inlet which allows flow of dialysate into a dialysate-side of said second filtering elements and the third end being associated with a second dialysate outlet which allows flow of dialysate out of the dialysate-side of said second filtering elements; and

an inter-stage connector connected to the second end of the first housing and to the third end of the second housing and adapted to allow flow of blood from the blood side of the first filtering elements to the blood-side of the second filtering elements,

wherein said inter-stage connector has a header space associated with the blood-side of the first filtering elements, with the blood-side of the second filtering elements, and with a substitution-fluid inlet which allows flow of substitution fluid into said header space thereby to dilute the blood in said header space.

2. A dual-stage hemodiafiltration cartridge according to claim 1 wherein said inter-stage connector comprises an inter-dialysate port including said first dialysate inlet and said second dialysate outlet.

3. A dual-stage hemodiafiltration cartridge according to claim 2 comprising an inter-aperture cap mounted on said inter-dialysate port and structured to allow flow of dialysate directly from the second dialysate outlet to the first dialysate inlet.

4. A hemodiafiltration system comprising:

a dual-stage hemodiafiltration cartridge according to claim 1; and

a control mechanism adapted to receive dialysate from the second dialysate outlet and to supply dialysate to the first dialysate inlet,

wherein said control mechanism controls the relative toxin removal rates of said first and second hemodiafiltration stages.

FIG. 1A

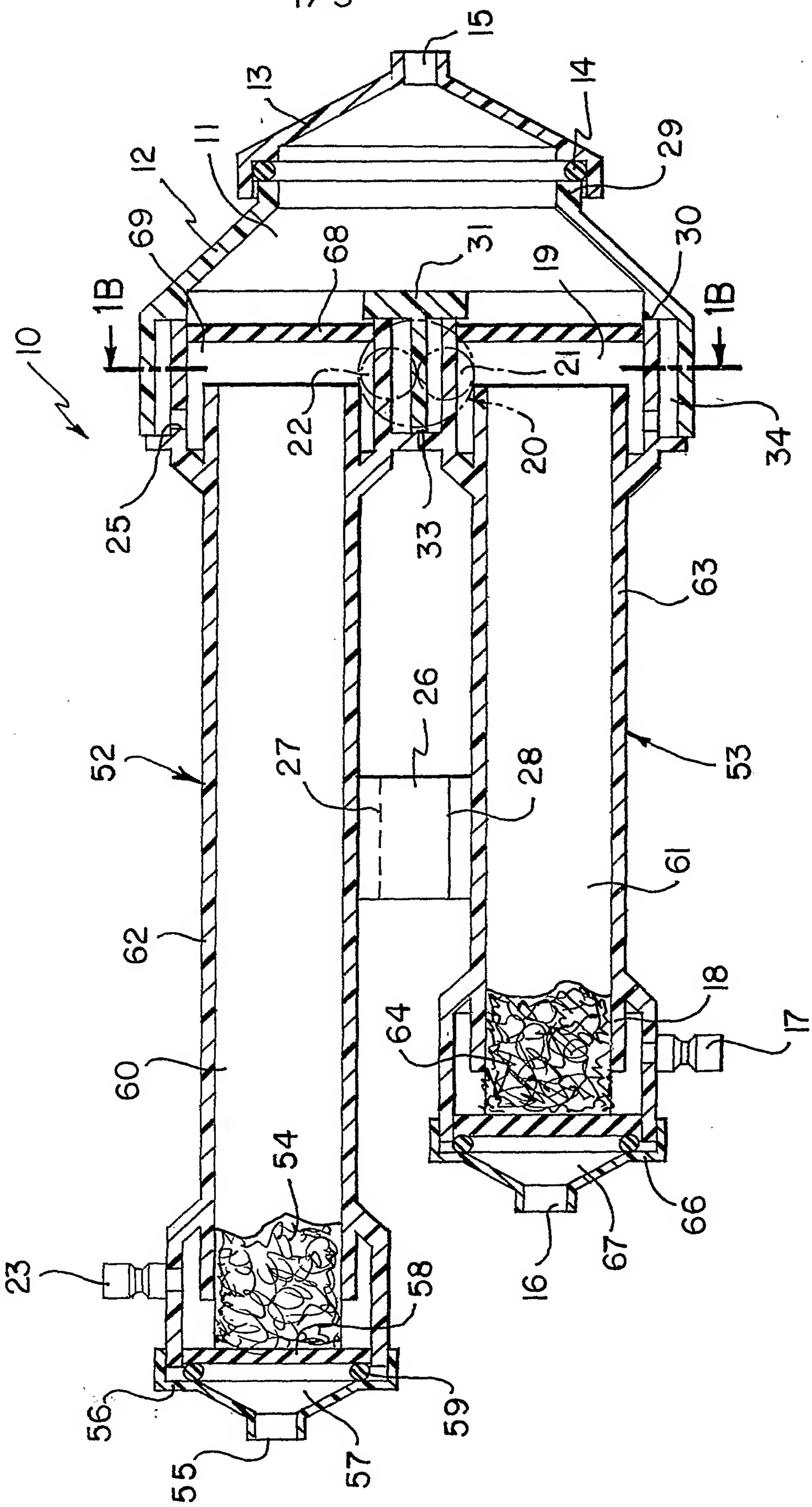
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FIG. 1B

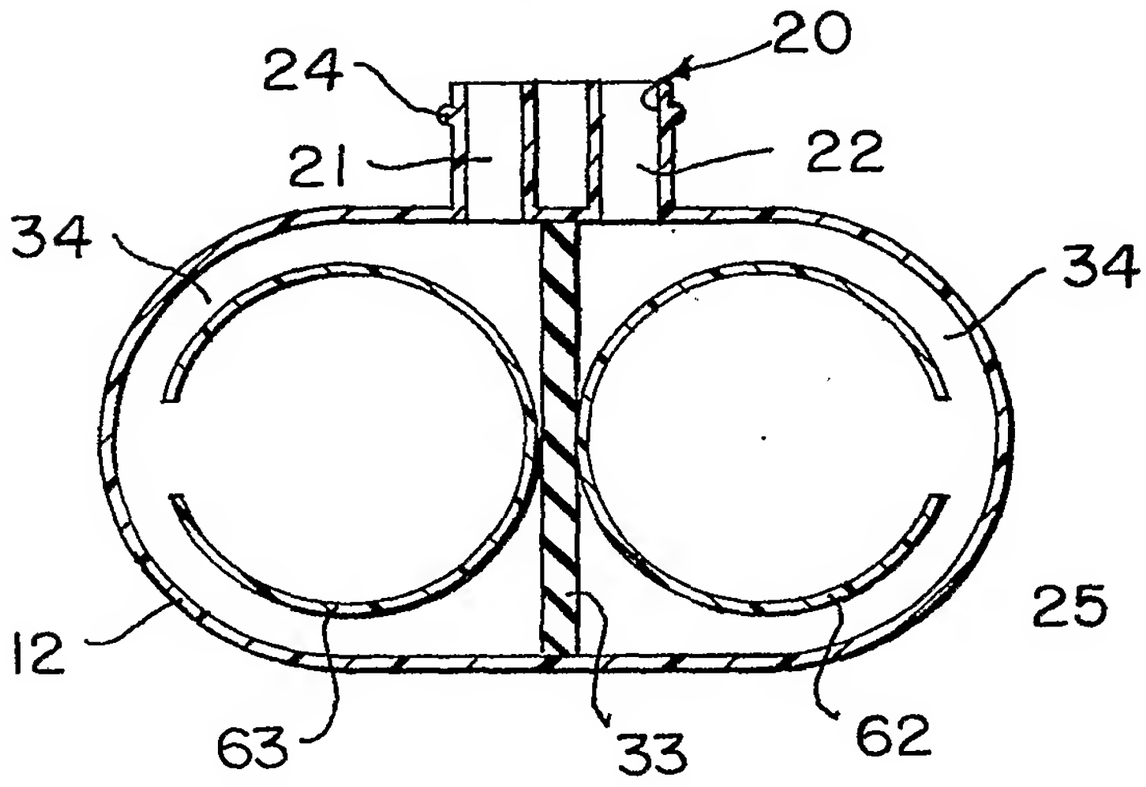


FIG. 2B

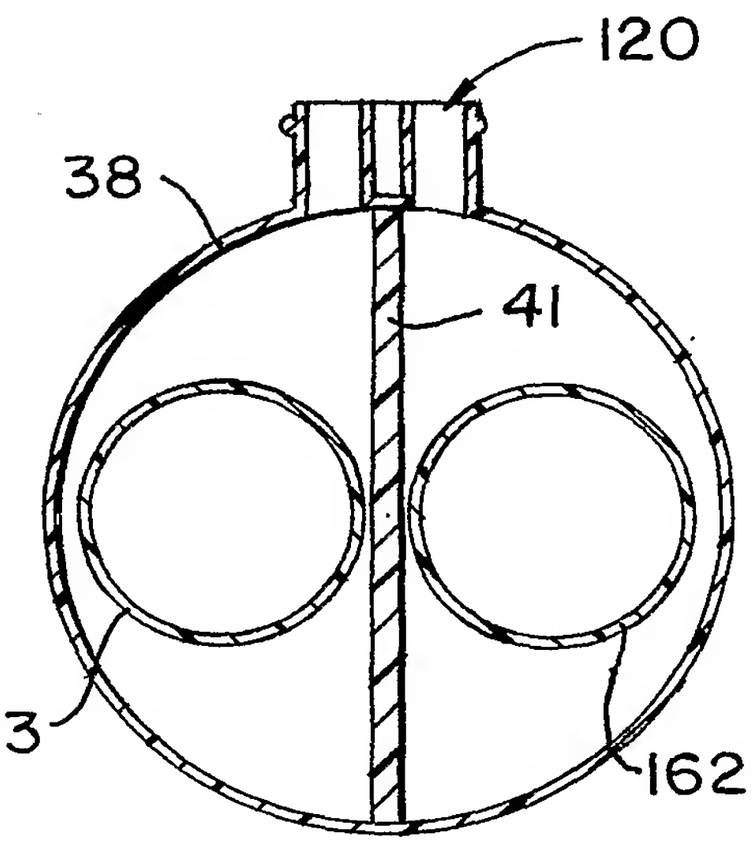


FIG. 3A

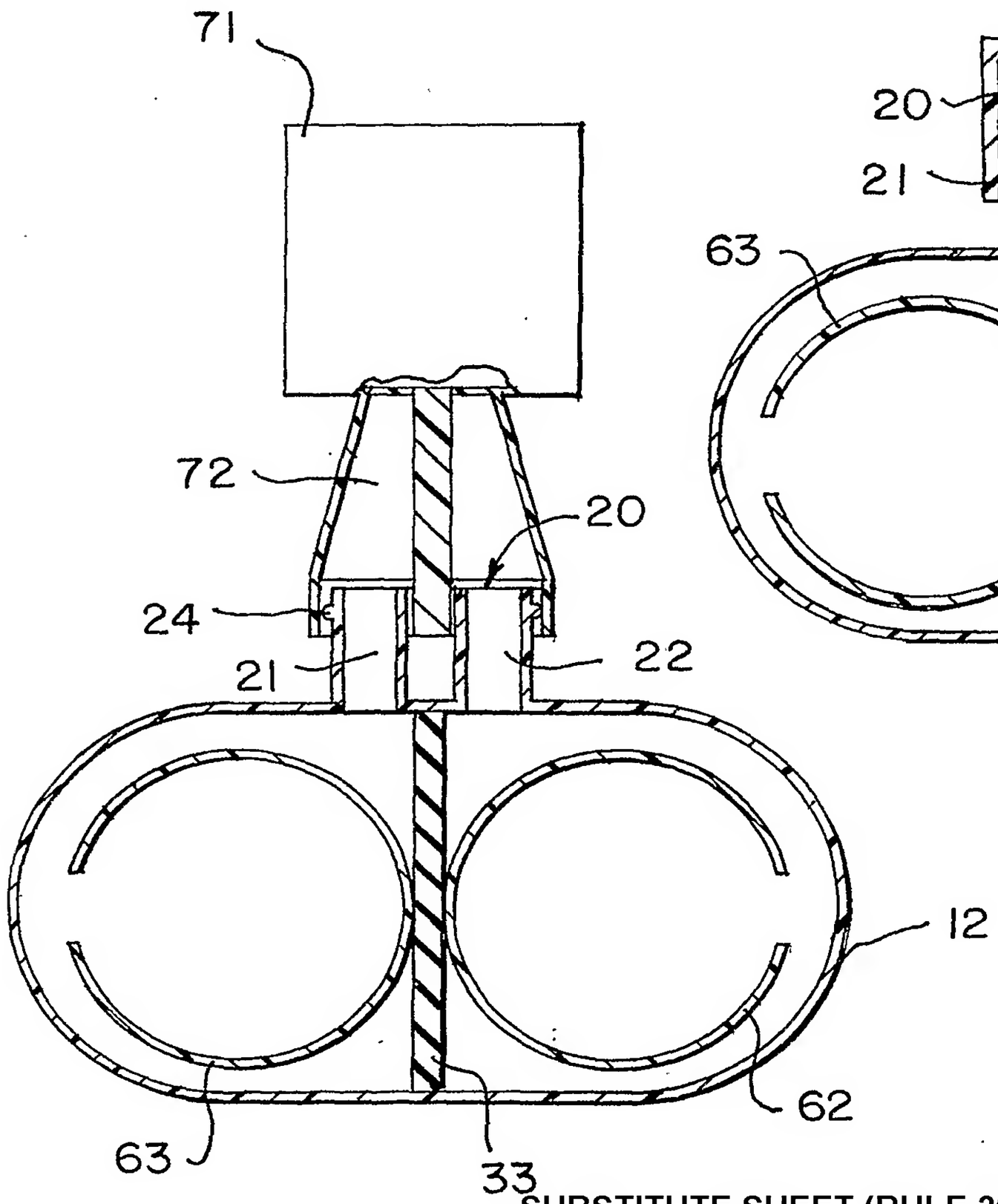
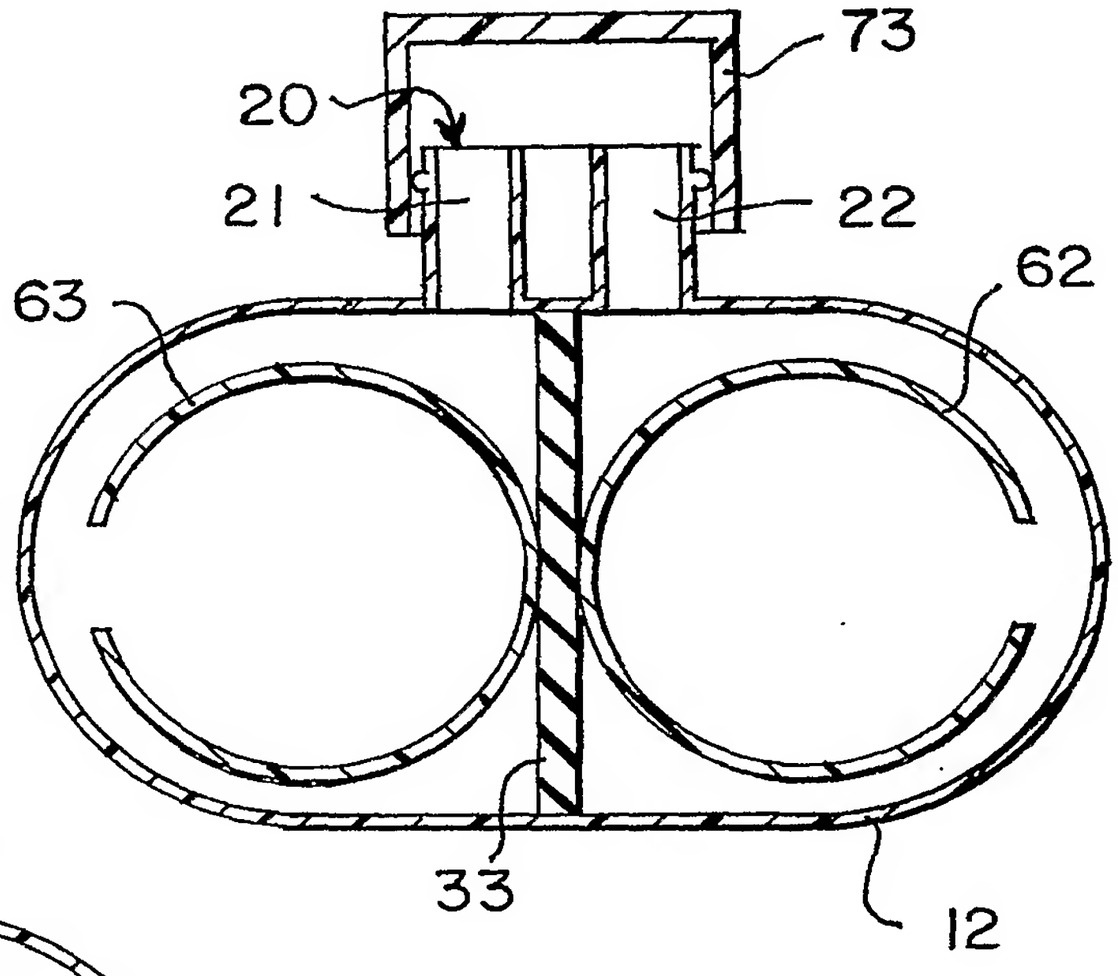


FIG. 3B



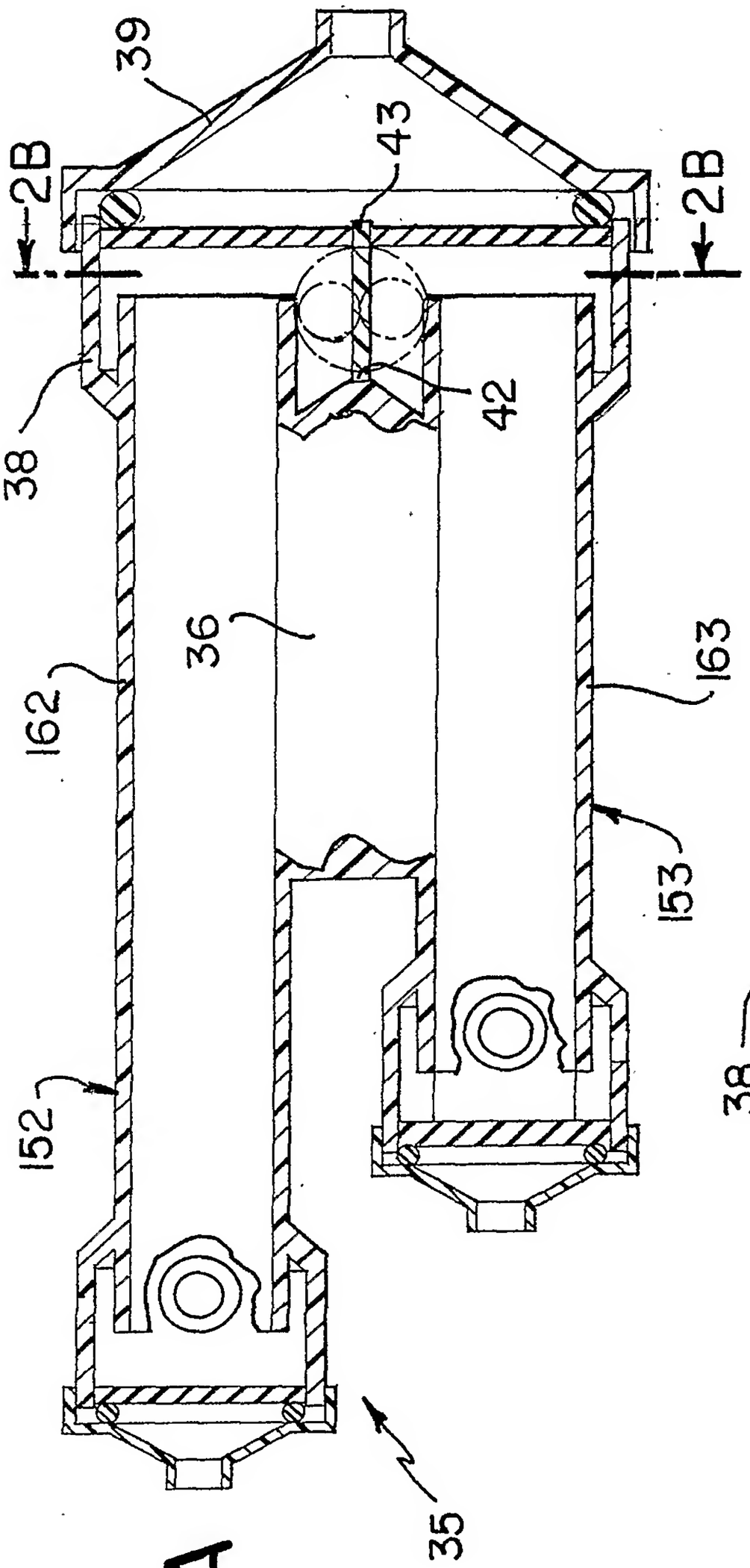


FIG. 2A

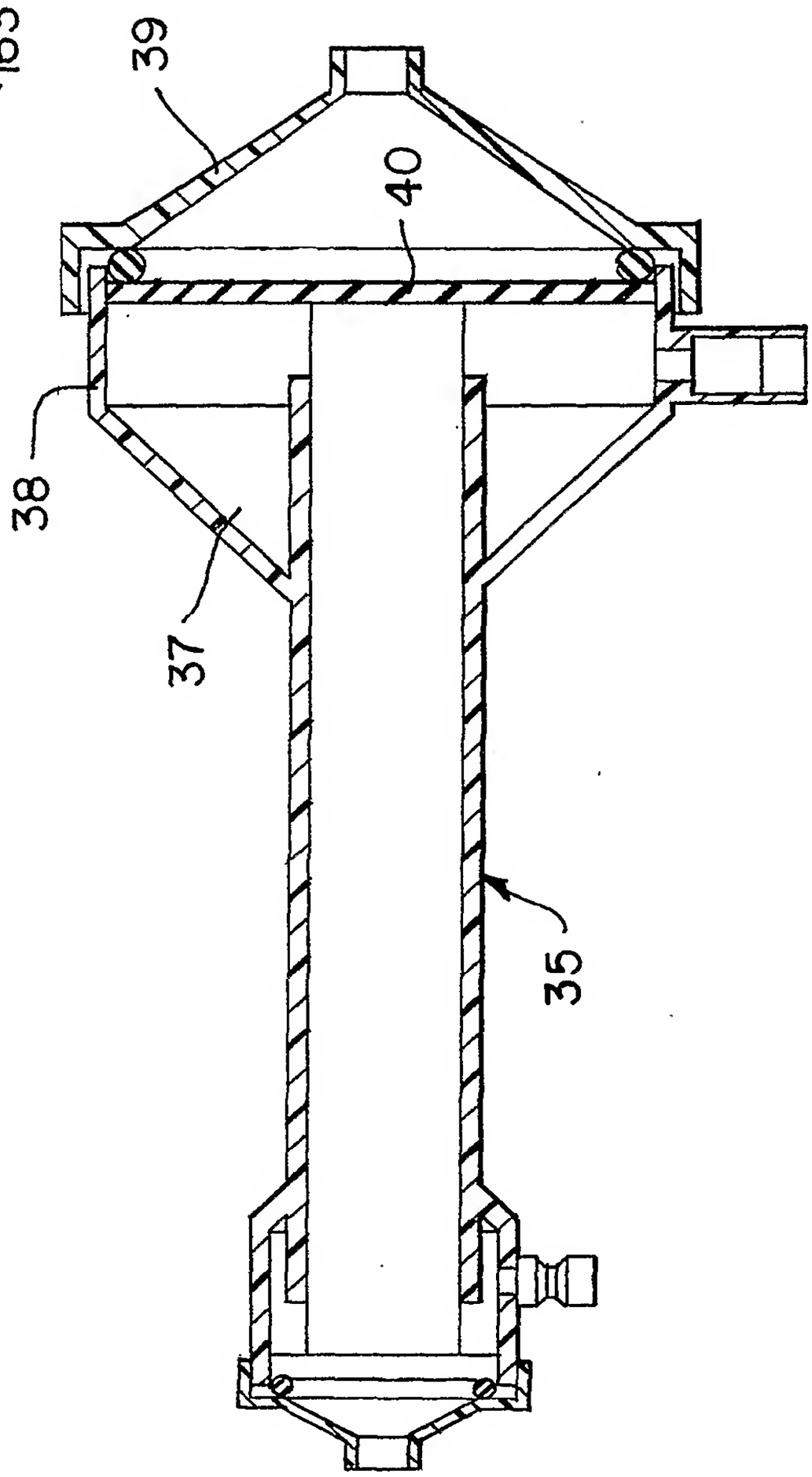


FIG. 2C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/35717

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : B01D 63/04
US CL : 210/96.2, 252, 321.71
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 210/96.2, 252, 321.71, 645, 646, 640, 321.6, 257.2, 420, 323.1, 323.2, 321.78, 321.79, 321.80, 321.87, 321.88, 321.89, 604/6.09

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EAST
search terms: haemodiafiltration, hemodiafiltration, end stage, renal disease

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,075,003 A (AOYAGI) 24 December 1991, figures 3 and 4.	1
Y	US 5,194,157 A (GHEZZI et al) 16 March 1993, col. 3, lines 19-22 and figure 1.	1
Y	US 5,660,772 A (NEDERLOF) 26 August 1997, abstract.	2, 4

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search 08 FEBRUARY 2001	Date of mailing of the international search report 26 APR 2001
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